REMARKS

Applicant thanks Examiners Zara, Shuklar, and LeGuyader for the courtesies extended during the personal interview held with the undersigned on 24 Febuary 2004.

Claims 1, 21, and 28-32 are pending. Claims 2-20, 22-27, and 33-43 have been cancelled in this or prior amendments. Claims 1, 21, and 28-29 are currently amended. These claims have been cancelled or amended without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file continuation applications directed to the subject matter of any claim cancelled for any reason.

The amendments to the pending claims are made to more clearly define the inventions. It is submitted that the amendments introduce no new matter and entry of the same is respectfully requested. By these amendments, the Applicant does not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which the Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

I. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Claims 1, 4-7, 11, 19-21 and 27-32 are rejected under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 1, 4-7, 11, 19-21 and 27-32 under 3 U.S.C. § 112, first paragraph for lack of written description. Office Action mailed 7 April 2004, page 2. Applicant respectfully traverses.

In addition, the Examiner maintained the rejection of claims 1, 4-7, 11, 19-21 and 27-32 under 35 U.S.C. § 112, first paragraph, for lack of enablement. *See id.* at pages 3-4. Specifically, the Examiner alleges that "it would take undue experimentation to utilize existing methodologies to identify all, or a representative number of species of the broad genus comprising all cis acting sequences that mediate the transcription of any hyphal specific genes in *C. albicans*, whereby *C. albicans* growth is inhibited." *Id.* at page 4. Applicant respectfully traverses.

As explained in more detail below, the declaration of Paula R. Sundstrom, Ph.D. and its associated evidence (the "Sundstrom Declaration") demonstrate that the specification of the referenced application fully describes and enables one skilled in the art to practice the presently claimed inventions, under 35 U.S.C. § 112, first paragraph.

Specifically, Dr. Sundstrom attests that she is the inventor of the subject matter disclosed and claimed in the referenced patent application. Sundstrom Decl., ¶ 1. She has read and is familiar with the Office Action mailed 7 April 2004 pertaining to the referenced application. *Id.* at ¶2. She understands that in the Office Action mailed 7 April 2004 the Examiner rejected claims 1, 4-7, 11, 19-21 and 27-32 under 35 U.S.C. § 112, first paragraph, for lack of written description and enablement. *Id.*

Dr. Sundstrom further attests that she has also read and is familiar with the concurrently-filed Amendment and Reply under 37 C.F.R. § 1.111. *Id.* at ¶3. Specifically, she has reviewed the claims as amended and she declares that currently amended claim 1 reads as follows:

> "A method comprising the step of:
>
> inhibiting attachment of *C. albicans* to human tissue by interfering with DNA binding proteins specific to UAS regions of the promoter of *HWP1* present during germ tube formation in said *C. albicans*."

Id.

Dr. Sundstrom further states that the specification of the referenced application and, specifically, the experiments described therein as supported by the data presented herein, fully describe and enable, in her opinion, one skilled in the art to practice the claimed inventions, including inhibiting attachment of *C. albicans* to human tissue by interfering with DNA binding proteins specific to UAS regions of the promoter of *HWP1* present during germ tube formation in *C. albicans*. *Id.* at ¶4. Dr. Sundstrom refers to portions of the specification that support her opinion, for example, pages 1-2, 6, 8, 10-11, 21-22, 24, 26, 53, 55, 62, 64-68, 72, and 75 of the specification. *Id.* Dr. Sundstrom attests that her opinion is also supported by Figures 1-5, which are attached to the Sundstrom Declaration. *Id.* Dr. Sundstrom concludes that, in her opinion, the present specification fully describes the inventions defined in the presently submitted amended claims and enables one skilled in the art to make and use those claimed inventions. *Id.*

Dr. Sundstrom states that experiments described in the referenced application and subsequently performed in her laboratory, at her direction, using Green Fluorescent Protein ("GFP") as a reporter to assess the role of sequences upstream of the coding region show that specific UAS regions denoted "Morphogenic Response Region 1" ("MRR1") and "Morphogenic Response Region 2" ("MRR2") mediate expression of the *HWP1* gene in response to hypha-inducing conditions. *Id.* at ¶ 5. Dr. Sundstrom refers to Figure 4 attached to her declaration and attests that deletion of DNA containing these regions leads to a 97%

reduction in promoter activity as assessed by GFP expression relative to wild type. *Id.* "Without DNA sequences upstream of *HWP1* inclusive of these activating regions, the *HWP1* gene itself is not expressed." *Id.*

Furthermore, Dr. Sundstrom declares that "the following evidences that *C. albicans* germ tubes, the predecessors of true hyphae, contain proteins that bind to these UAS regions of the *HWP1* promoter." *Id.* at ¶6. Dr. Sundstrom states that the presence of these proteins in germ tubes and not yeast is important because expression of the *HWP1* gene occurs in germ tubes and true hyphae but not in yeast. *Id.* "Specific factors responsible for this morphogenetic regulation are predicted to be present in germ tubes and absent in yeasts." *Id.* Dr. Sundstrom concludes that the presence of specific regions of activation, as shown in the specification and supported by her declaration, coupled with evidence of such DNA binding proteins in germ tubes supports the presently claimed invention. *Id.*

With regard to the promoter deletion experiments described in the referenced application, Dr. Sundstrom states that strains with maximal *HWP1* promoter activity, defined as 100%, were created by integration of the GFP reporter construct at the native *HWP1* locus where GFP expression was under the control of the entire region upstream of the transcription start site. *Id.* at ¶ 7. Figure 5 attached to the Sundstrom declaration shows the nucleotide sequence of the *HWP1* promoter. *Id.* "Integration at an ectopic site, the ENO1 locus, of wild type promoter constructs or constructs with external and internal deletions was performed to identify specific regions within the promoter that were important for GFP expression." *Id.*

Dr. Sundstrom provides Figures 1A-1B which presents the results from her functional characterization of the *HWP1* promoter by analysis of external and internal deletion derivatives described in the specification and in Paragraph 7 of her Declaration. *Id.* at ¶8. "Figure 1A shows fluorescence intensities of strains were determined in TCM199 after 3 h of growth at 37 °C. Values represent % of fluorescence of strains with the GFP reporter controlled by the entire *HWP1* promoter at its native locus (HB-12). The horizontal green bar indicates *HWP1* promoter DNA. The blue diamond indicates the position of the transcription start site. The vertical red bar just upstream of the blue diamond within the green bar signifies a TATAA element. Gaps connected by thin red lines indicate deleted regions." *Id.*

Dr. Sundstrom refers to Figure 1A and states that the fluorescence intensities of strains containing a construct 1902 bp upstream of the transcription start site were over 90% of the maximal promoter indicating that the sequences most responsible for promoter activation were found within this region (Construct –1902). *Id.* at ¶9. She points out that analysis of the other deletion derivatives (Figure 1A) showed that important activating

regions were located between 1 and 2 kb upstream of the transcription start site in that deletion of 840 bp (-1063) resulted in a 97% reduction in fluorescence. *Id.* "A minor region of activation was found between -803 and -555 as shown by the reduction in fluorescence of 2.3% to 1.6%, the latter value being equivalent to the promoterless construct control." *Id.* Thus, Dr. Sundstrom concludes that sequences between -1063 and -555 conferred a basal level of promoter activity. *Id.*

Dr. Sundstrom discusses Figure 1B which is a graph showing fluorescence intensities of the various constructs relative to the wild type *HWP1* promoter. *Id.* at ¶10. She notes that a bimodal pattern of activation within the 840 bp region between nucleotides -1902 and -1063 was shown by strains with external deletions. *Id.* "A distal activating region extended from -1902 to -1410 and accounted for over 60% of promoter activity in that deletion of 493 bp (-1410) reduced fluorescence to 38.8% of promoter activity at the native locus." *Id.* Dr. Sundstrom further states that the proximal segment spanning nucleotides, -1410 to -1063 accounted for approximately 36% (38.8 - 2.6) of promoter activity. *Id.* Because most of the promoter activity in the distal segment was located within the first 246 nucleotides, as shown by the 45% decrease in activity for construct -1657 compared to -1902, Dr. Sundstrom denoted this region MRR1. *Id.* "Over half of the 45% decrease was attributable to the 125 nucleotides between -1782 and – 1657 (72.3-45.7/45). An internal deletion of this region led to a 31% reduction in promoter activity (Construct L, Figure 1A)." *Id.*

Dr. Sundstrom found a more proximal region of activation relative to the transcription start site spanning nucleotides -1410 to –1042. *Id.* at ¶ 11. She attests that the function in activating expression was demonstrated by fusing this region to fragments with only basal promoter activity (external deletion - 555 (Construct E, Figure 1A) and external deletion -803 (Construct C, Figure 1A)). *Id.* "Fluorescence intensities of 85 and 73%, for strains C and E, respectively relative to external deletion –1410 were found. Eleven percent of the fluorescence intensity of construct –1410 was present in strains with a fusion of segment -1288 to -1042 to external deletion -555 (Construct K2, Figure 1A)." *Id.* Dr. Sundstrom also states that the 3' boundary of the proximal activating region was tested in constructs A and B, with 3' ends at -1130 or –1042, respectively, fused to external deletion -871 having basal promoter activity. *Id.* She notes that fluorescence intensity attributable to construct A was 30% of fragment B reflecting the importance of nucleotides between -1130 and -1042. *Id.* Therefore, Dr. Sundstrom denoted the region between -1410 and -1042 MRR2. *Id.* "Included within MRR2 was a repressing region between nucleotides -1410 and –1366 as

shown by the increase in intensity from 38.8% to 58.7% for the two external deletions. This regulatory region within UAS MRR2 was termed MRR2a." *Id.*

To show the importance of such UAS regions in controlling expression of Hwp1 during germ tube formation, Dr. Sundstrom transformed an *hwp1/hwp1* null strain with a promoterless *HWP1* gene targeted to the *ENO1* locus created. *Id.* at ¶12. She refers to Figure 2 which illustrates the effect of the promoter deletion on Hwp1 expression. *Id.* She states that indirect immunofluorescence assay using anti-Hwp1 antibodies was used to detect Hwp1 on germ tubes. *Id.* "Photographs were taken with 644 msec exposure times. SC5314 and the *hwp1/hwp1* null mutant which lacks the *HWP1* coding region are shown in A and B." *Id.* Dr. Sundstrom declares that the strains shown in C and D have the complete coding region of *HWP1* integrated at the *ENO1* locus; however, the strain shown in D lacks the *HWP1* promoter region. *Id.*

Dr. Sundstrom then refers to Figure 2 and attests that Hwp1 was not present as deduced by anti-Hwp1 antibody in an indirect immunofluorescence assay. *Id.* at ¶ 13. "The control strain, which was constructed similarly except that –1902 bp of *HWP1* upstream region was included, produced abundant Hwp1, showing that upstream sequences harboring UAS MRR1 and MRR2 are required for production of Hwp1 and its associated virulence attributes." *Id.*

Dr. Sundstrom further declares that to search for DNA-binding proteins specific to the cis-activating regions (UAS regions), electrophoretic mobility shift (EMSA) experiments were performed. *Id.* at ¶14. She states that the DNA fragments used in the analysis are shown in Figures 3A-3B. *Id.* "Results for MRR1 show the presence of DNA binding proteins that bind to the UAS MRR1 region of the promoter of *C. albicans* during germ tube formation."..*Id.*

Dr. Sundstrom provides Figure 3A which is a diagram representing regions used in EMSA analysis. *Id.* at ¶15. "Fragments with stars gave positive results in EMSA analyses, and therefore bind proteins in crude extracts of *C. albicans*." *Id.* Dr. Sundstrom states that stippled stars denote fragments shifted in both yeast and germ tube extracts whereas the fragment denoted by the solid star is positive with germ tube extracts only. *Id.* She then refers to Figure 3B which depicts EMSA analysis using PCR fragments from distal regions of the *HWP1* promoter diagrammed above. Dr. Sundstrom attests that the shifted band denoted by the solid star is found in germ tube extracts but not in yeast extracts. *Id.* "The shifted band is specific as it is competed by unlabeled specific DNA but not by non-specific DNA." *Id.*

Dr. Sundstrom further declares that "[i]n light of the foregoing, in my opinion, the specification of the referenced application fully describes the presently claimed invention and enables a person skilled in the art to make and use the claimed invention." *Id.* at ¶ 16. She concludes that the specification of the referenced application and the supporting data presented herein fully describe and enable one skilled in the art to make and use the claimed inventions, including inhibiting attachment of *C. albicans* to human tissue by interfering with DNA binding proteins specific to UAS regions of the promoter of *HWP1* present during germ tube formation in *C. albicans*." *Id.*

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the present rejections of the claims under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicant has properly and fully addressed each of the Examiner's grounds for rejection. Applicant submits that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited.

If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully submitted,

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7 July 2004

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